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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,809	10/05/2001	Sundeep Khosla	07039-322001	4349

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/972,809	Applicant(s) KHOSLA ET AL.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25-37* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

The Sequence Listing filed October 5, 2001 was not accompanied by a statement under 37 CFR 1.821(f) stating that the content of the paper copy and computer readable form copy of the sequence listing are the same.

Correction is required.

The Sequence Listing filed October 5, 2001 was approved by STIC for matters of form.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for targeting an IGFII polypeptide when the IGFII polypeptide is in the form of a complex with an IGFBP2 polypeptide, does not reasonably provide enablement for targeting in which the individual components are merely mixed or where the individual components are not even co-administered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among

these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. With respect to (1), the nature of the invention is therapeutic agents which target skeletal extracellular matrix of a patient. With respect to (2), the prior art does not show that components of a therapeutic composition which are merely mixed together or which are not even co-administered will stay together and arrive at the same location within a patient upon administration. With respect to (3), the relative skill of those in the art is high. With respect to (4), while the predictability of the covalent conjugate art is high, there is no predictability or expectation that the mere physical admixture of components of a therapeutic composition is sufficient to cause the components to stay together and arrive at the same location within a patient upon administration. With respect to (5), the method claims embrace the administration of physical admixtures of components. With respect to (6) and (7), there is no direction or guidance or working examples directed towards the use of physical admixtures of the components. No theory or scientific rationale is presented as to how physical admixtures of the components would target the same locations within a patient. The examples of the specification are directed solely to the use of complexes, with the possible exception of Example 11. Example 11 is silent as to whether complexes have formed in the mixtures which are administered to the rats. Further, Example 11 is silent as to whether targeting has occurred (as opposed to contact of the IGFII polypeptide with the intended tissues as a result of random circulation and diffusion of the administered IGFII polypeptide). With respect to (8), vast amounts of experimentation would be necessary in order to practice the

invention, especially in view of the lack of predictability in the art and the lack of direction or guidance or working examples. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-23 and 25-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 5,998,369. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '369 patent anticipate instant claims 1, 2, 4, 10-15, 17, 18, 20-23, 26, 27, 33, and 35-37. With respect to instant claims 3, 16, 19, 25, and 34, while the '369 patent claims IGFII, the '369 patent does not claim human IGFII. It would have been obvious to one of ordinary skill in the art to use human IGFII as the source of the IGFII required by the claims of the '369 patent because use of the human source would permit the treatment of human patients while lessening the possibility of adverse immunological reactions. With respect to instant claims 5-9 and 28-32, while the '369 patent does not claim these specific methods of administration, it would have been obvious to one of ordinary skill in the art to administer the

complexes claimed in the '369 patent by the specific methods recited in instant claims 5-9 and 28-32, because these specific methods are known methods of administering proteins to humans and because it is routine in the art to administer proteins by methods known in the art to be useful for administering other proteins.

5. Claims 1-23 and 25-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 and 22-33 of copending Application No. 09/428,226. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '226 application anticipate instant claims 1, 2, 4-15, 17, 18, 20-22, 26-33, and 35-37. With respect to instant claims 3, 16, 19, 25, and 34, while the '226 application claims IGFII, the '226 application does not claim human IGFII. It would have been obvious to one of ordinary skill in the art to use human IGFII as the source of the IGFII required by the claims of the '226 application because use of the human source would permit the treatment of human patients while lessening the possibility of adverse immunological reactions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-23 and 25-37 are directed to an invention not patentably distinct from claims of commonly assigned 5,998,369. Specifically, see the above obviousness-type double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 5,998,369, discussed above, would form the basis for a

rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

7. The effective filing date of instant claims 1, 2, 4, 5, 8, 10, 15, 18, 20, and 22 is deemed to be at least May 5, 1998, the filing date of grandparent application 09/073,032. These claims are deemed to be entitled under 35 U.S.C. 120 to the benefit of the filing date of the '032 application because the '032 application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

The effective filing date of instant claims 3, 6, 7, 9, 11-14, 16, 17, 19, 21, and 23-37 is deemed to be October 5, 2001, the filing date of the instant application. Instant claims 3, 6, 7, 9, 11-14, 16, 17, 19, 21, and 23-37 are not deemed to be entitled under 35 U.S.C. 120 to the benefit of the filing date of grandparent application 09/073,032 or of parent application 09/428,226 because the '032 application and the '226 application, under the test of 35 U.S.C. 112, first paragraph, do not disclose human IGFII, do not disclose intravenous, subcutaneous, or

intramuscular administration of the IGFII and IGFBP2 polypeptides, do not disclose administration of the IGFII and IGFBP2 polypeptides via an implanted device, do not disclose administration of the IGFII and IGFBP2 polypeptides to a mucous membrane, do not disclose complexes comprised of a compound, an IGFBP2 polypeptide, and an IGFII polypeptide (the applications' disclosures of 3-component complexes including compounds are limited to IGFIIE polypeptides), and do not disclose therapeutic methods, pharmaceutical compositions, or articles of manufacture involving IGFII and IGFBP2 polypeptides in non-complexed forms. Accordingly, U.S. Patent No. 5,998,369, which issued based upon grandparent application 09/073,032 and which has a different inventorship than the instant application, is available as prior art against instant claims 3, 6, 7, 9, 11-14, 16, 17, 19, 21, and 23-37 under 35 U.S.C. 102(b).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

9. Claims 6, 7, 11-14, 17, 21, 23, 26-31, 33, and 35-37 are rejected under 35 U.S.C. 102(b) as being anticipated by the U.S. Patent No. 5,998,369. See the above obviousness-type double patenting rejection. In addition, the U.S. Patent No. 5,998,369 teaches intranasal administration and administration using osmotic pumps and implantable infusion systems (see, e.g., column 7, lines 4-5, 16-17, and 21-24).

10. Claims 3, 9, 16, 19, 25, 32, and 34 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,998,369. See the above obviousness-type double patenting rejection.

11. Claims 18, 19, 33, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by the Bach et al article (Biochim. Biophys. Acta, Vol. 1313, pages 79-88). The Bach et al article teaches the formation and separation of recombinant human IGF-II and IGFBP2 complexes in buffered aqueous solutions optionally comprising 0.5 M NaCl. See, e.g., sections 2.2.2, 2.2.3, 2.2.5, and 2.2.6. IGF-II is a fragment of full-length IGFIIE polypeptide. Because the same components are being contacted and complexed in the Bach et al article as are claimed by Applicants, inherently the Bach et al article will form complexes of IGF-II and IGFBP2 in the

same molar ratios claimed by Applicants. In view of the breadth of the claim terminology "amount effective" and in view of the breadth of the claim terminology "mammal", the amounts of complex formed in the Bach et al article are deemed inherently to satisfy the amounts required by instant claims 18 and 33. Sufficient evidence of similarity is deemed to be present between the complexes in buffered aqueous solution of the Bach et al article and Applicants' claimed compositions to shift the burden to Applicants to provide evidence that their claimed compositions are unobviously different than those of the Bach et al article.

12. Claims 1, 4-6, 11, 18, 21-23, 27-29, 33, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Clark et al (U.S. Patent No. 5,187,151). Clark et al teach subcutaneous administration of a complex of IGF-I, IGFBP-3, and ALS in order to grow bones, e.g., for the treatment of osteoporosis. The compositions are stored in unit or multi-dose containers. See, e.g., column 4, lines 53-55; column 6, lines 64-68; column 7, lines 26-33; column 8, lines 2-4; column 9, lines 12-16; and column 12, lines 39-40. The IGF-I and IGFBP-3 of Clark et al correspond to Applicants' "IGFII polypeptide" and "IGFBP2 polypeptide", respectively, because Applicants define their polypeptides as including functional equivalents (see page 5, lines 3-11, of the specification) and because Clark et al's IGF-I and IGFBP-3 have the equivalent functions of binding to one another, increasing bone growth, and being suitable for the treatment of osteoporosis. With respect to instant claim 11, the ALS present in the complex of Clark et al corresponds to Applicants' compound. Because the same active agents are being administered by the same method steps to the same patient, inherently the ALS of Clark et al will be targeted to skeletal extracellular matrix in Clark et al to the same extent claimed by Applicants.

13. Claims 1, 2, 4-6, 11, 12, 18, 20-23, 27-29, 33, 36, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Clark et al (U.S. Patent No. 5,187,151). Application of Clark et al is the same as in the above rejection of claims 1, 4-6, 11, 18, 21-23, 27-29, 33, and 37. Clark et al disclose the use of IGFBPs in general (see, e.g., column 7, lines 26-27), and list IGFBP-2 as a useful IGFBP (see, e.g., column 6, lines 6-21), but do not specifically exemplify IGF-I in combination with IGFBP-2. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use IGFBP-2 to form the complexes of Clark et al because Clark et al disclose IGFBP-2 to be a useful source of the IGFBP required by Clark et al, and because the substitution of one known functional equivalent for another with only the expected result that the complex can be used to increase bone mass and to treat osteoporosis patients is prima facie obvious. With respect to claims 20 and 36, while Clark et al teach their active agents in packaged forms, Clark et al do not teach including a label or insert with instructions for use in the package. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to include a label or insert with instructions for use in the package of Clark et al because such a label or insert is a standard component in pharmaceutical packages and would have been expected to be useful in aiding the practitioner to administer the active agents correctly.

14. Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Both U.S. Patent No. 5,998,369 and Clark et al (U.S. Patent No. 5,187,151) teach administering the IGF and IGFBP in the form of a complex, and do not teach or suggest separately administering these components.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

April 1, 2003